TRPC channels in cardiac plasticity

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Abstract:
Cardiac plasticity, defined as structural remodeling of the heart in response to environmental demands, is an intrinsic compensatory mechanism to maintain hemodynamic workload. Both hypertrophied and atrophied myocardium exhibit reduced contractility due to decreased myocardial flexibility. Our laboratory studies on the common mechanism underlying reduction of myocardial flexibility due to hemodynamic loading and unloading, and aims to establish novel therapeutic strategies for realization of a "society of health and longevity". We used doxorubicin (DOX), a highly effective anticancer agent but induces myocardial atrophy, for investigating molecular mechanism of myocardial atrophy. We found that transient receptor potential canonical 3 (TRPC3) channels participate in DOX-induced myocardial atrophy in mice. DOX increased production of reactive oxygen species (ROS) in rodent cardiomyocytes through hypoxic stress-mediated upregulation of NADPH oxidase 2 (Nox2), which formed a stable complex with TRPC3. Specific inhibition of TRPC3-Nox2 coupling suppressed DOX-induced myocardial atrophy and left ventricular (LV) dysfunction and its upregulation of Nox2 and oxidative stress, without reducing hypoxic stress. Downregulation of the TRPC3-Nox2 complex through voluntary exercise promoted volume load-induced LV compliance and flexibility with physiological hypertrophic growth of the myocardium. As the prevention of cellular toxicity by inhibition of TRPC3-Nox2 complex also seemed to be applicable to macrophage and skeletal muscle cells, these results illustrate the impact of TRPC3 on LV compliance and flexibility and, focusing on the TRPC3-Nox2 complex, provide a new strategy for maintaining cardiocirculatory homeostasis.